Docket No.: 13173-00010-US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Holger Puchta et al.

Confirmation No.: 2084

Application No.: 10/750,891

Group Art Unit: 1638

Filed: January 5, 2004

Examiner: Li Zheng

For: RECOMBINATION SYSTEMS AND METHODS FOR ELIMINATING NUCLEIC ACID SEQUENCES FROM THE GENOME OF EUKARYOTIC ORGANISMS

BRIEF ON APPEAL

TABLE OF CONTENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of: Holger Puchta et al.	Confirmation No.: 2084
Application No.: 10/750,891	Group Art Unit: 1638
Filed: January 5, 2004	Examiner: Li Zheng

For: RECOMBINATION SYSTEMS AND METHODS FOR ELIMINATING NUCLEIC ACID SEQUENCES FROM THE GENOME OF EUKARYOTIC ORGANISMS

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby appeal the Examiner's decision rejecting claims 1-4 and 27-28 as set forth in the Office Action of September 30, 2008.

As required under 37 C.F.R. § 41.37(a), this brief is filed within two months of the filing of the Notice of Appeal, which was filed on February 27, 2009, with the required fee authorization pursuant to § 41.20(b)(2).

I. REAL PARTY IN INTEREST

The real parties in interest are SunGene GmbH & KGaA and Institut f. Pflanzengenetik u. Kulturpflanzenforschung ("SunGene"), the assignees of record.

II. RELATED APPEALS, INTERFERENCES, AND JUDICIAL PROCEEDINGS

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 30 claims pending in application.

B. Current Status of Claims

Claims cancelled: none

Claims withdrawn from consideration but not canceled: 5-26 and 29-30

Claims pending: 1-30

Claims allowed: none

Claims rejected: 1-4, and 27-28

Claims objected to: none

C. Claims On Appeal

The claims on appeal are claims 1-4, and 27-28

A copy of the appealed claims as they currently stand is provided in Section VIII as Appendix A.

IV. STATUS OF AMENDMENTS

Applicant filed an Amendment After Final Rejection on December 30, 2008. The Examiner responded to the Amendment After Final Rejection in an Advisory Action mailed February 17, 2009. In the Advisory Action, the Examiner indicated that Applicants' proposed cancellation of claim 23 and new claim 31 would not be entered.

Accordingly, the claims enclosed herein as Appendix A do not incorporate either the cancellation of claim 23 or the new proposed claim 31.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Of the 6 claims on appeal, claim 1 is the only independent claim. Claim 1 and the claims dependent therefrom (claims 2, 4, and 27-28) and dependent claim 3 will be argued separately. Claims 1 and 3 are as follows:

Claim 1 provides:

A recombination system for repeated, successive application within the same organism (p. 6-7, ¶¶[0019]-[0020]) comprising:

a transgenic recombination construct capable of being inserted into the chromosomal DNA of a eukaryotic organism said construct comprising in a 5'- to 3'-orientation (p. 6, ¶[0020]; p. 11-12, ¶¶[0053], [0063]; original claim 1);

a first homology sequence A (p. 6, ¶[0020]; p. 11-12, ¶¶[0054], [0058], [0064]; p. 54-58, ¶¶[00229]-[00244]; Figures 1-10; and original claim 1);

at least one recognition sequence for site-directed induction of DNA double-strand breaks where all recognition sequences for site-directed induction of DNA double-strand breaks are located between homology sequences A and B (p. 11-12, ¶¶[0053]-[0069]; p. 54-58, ¶¶[00229]-[00244], and Figures 1-10) and

a second homology sequence B (p. 6, ¶[0020]; p. 11-12, ¶¶[0056], [0061], [0068]; p. 54-58, ¶¶[00229]-[00244]; Figures 1-10; and original claim 1),

wherein the homology sequences A and B have at least 20 base pairs and at least 70% homology that allows for homologous recombination (p. 10, ¶¶[0048]-[0049]); and

an enzyme suitable for inducing DNA double-strand breaks at a recognition sequence for the site-directed induction of DNA double-strand breaks or a nucleic acid sequence encoding said enzyme (p. 6-7, ¶[0020]; p. 8, ¶[0038]; p. 13-18, ¶¶[0074]-[0096]; and original claim 1);

wherein after homologous recombination of homology sequences A and B the resulting transgenic sequence derived from said transgenic recombination construct does not comprise any recognition site for said enzyme suitable for inducing DNA double-strand breaks (p. 8-9, ¶¶[0038], [0040]; p. 47-48, ¶[00214]; p. 54-58, ¶¶[00229]-[00244], and Figures 1-10).

Claim 3 requires all the features of claims 1 and 2 (after said first homology sequence, contains a further nucleic acid sequence) and wherein the construct further contains a second recognition sequence for the site-directed induction of DNA double-strand breaks (p. 12, ¶¶[0063]-[0069]; p. 54-58, ¶[00231]-[00244]; Figures 3-10].

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection for review on appeal are as follows:

Are claims 1-4 and 27-28 unpatentable under 35 U.S.C. § 103(a) as being obvious over Dujon *et al.* U.S. Patent No. 6,395,959 ("Dujon")?

VII. ARGUMENT

Are claims 1-4 and 27-28 unpatentable under 35 U.S.C. § 103(a) as being obvious over Dujon *et al.* U.S. Patent No. 6,395,959 ("Dujon")?

The claims are non-obvious over Dujon for the following reasons which will be explained in further detail below:

1) the Examiner's characterization of the structure allegedly taught in Dujon is inaccurate;

2) even if Dujon suggested the structure as characterized by the Examiner, Dujon does not teach or suggest all the claim limitations;

3) Dujon does not provide any suggestion or motivation for one skilled in the art to modify the structure of Dujon;

4) even if the structure were modified as suggested by the Examiner, one skilled in the art would not arrive at the claimed invention; and

5) the modification suggested by the Examiner renders the structure inoperable for its intended purpose.

Claims 1, 2, 4, and 27-28

Claims 1-4 and 27-28 were rejected under 35 U.S.C. § 103(a) as being obvious over Dujon *et al.* U.S. Patent No. 6,395,959 ("Dujon"). Applicants respectfully disagree and traverse the rejection for the reasons of record and for the following additional reasons.

1. The Examiner's characterization of the structure allegedly taught in Dujon is inaccurate.

The Examiner relies on the illustration in Figure 25B parts (1) and (2) of Dujon for allegedly teaching a recombination system comprising a vector having, in the 5' to 3' direction, a LTR sequence, a left I-SceI recognition site, a selection marker, another LTR sequence, a right I-SceI recognition site, and a second selection marker (see Office Action dated December 26, 2007, p. 3). Applicants respectfully disagree with the Examiner's characterization of Dujon.

Rather the only teaching in Dujon is either a vector having, in the 5' to 3' direction, a LTR sequence, a I-SceI recognition site, and a selection marker (a "LTR-I-SceI-selection marker unit"), or a vector comprising tandem repeats of such a LTR-I-SceI-selection marker unit (see Dujon, Figure 25A). The tandem repeats are separated by viral sequences containing the tk gene (see Dujon Figure 25B and the caption for Figure 25 at col. 7). Therefore, Dujon does not disclose a unit with two LTRs, two recognitions sites, and two selection markers or the order as suggested by the Examiner.

Furthermore, the Examiner equates the LTR sequence of each tandem repeat to two homologous regions A and B with the left I-SceI site allegedly located in between. The Examiner also alleges that the PhleoLacZ selection marker of each tandem repeat corresponds to two homologous regions A and B with the right I-SceI site allegedly located in between. However, contrary to the Examiner's assertion, the description of Figure 25 discloses that the LTR of each LTR-I-SceI-selection marker unit contains an I-Sce I recognition site and a PhleoLacZ gene (see Dujon, col. 7, ll. 1-23). The description of Figure 25 also discloses several times that the recognition sequence is located within the LTR region, rather than between homology sequences as characterized by the Examiner. Thus the endonuclease of Dujon cuts within the LTR, not in between two homology sequences as characterized by the Examiner.

For these reasons, the Examiner's characterization of Dujon is contrary to its teaching.

2. Even if Dujon suggested the structure as characterized by the Examiner, Dujon does not teach or suggest all the claim limitations.

Assuming *arguendo* that the structure of Dujon comprises a vector having, in the 5' to 3' direction, a LTR sequence, a left I-SceI recognition site, a selection marker, another LTR sequence, a right I-SceI recognition site, and a second selection marker as characterized by the Examiner, Dujon still does not disclose or suggest all the limitations of the claimed invention.

The examiner bears the initial burden of establishing *prima facie* obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See *In re Lowry*, 32 F.3d 1579, 1582 (Fed. Cir. 1994).

Appellant's recombination system and method enables the predictable elimination of defined nucleic acid sequences from the chromosomal DNA of a eukaryotic organism and allows the repeated, successive application to the same organism, which has not been addressed by other systems (p. 6, ¶¶[0017], [0019]). The present system relates to a recombination system for repeated, successive application within the same organism, which comprises a transgenic recombination construct inserted into the chromosomal DNA of a eukaryotic organism comprising a sequence consisting, in the 5'/3'-direction, of a first homology sequence A, at least one recognition sequence for the site-directed induction of DNA double-strand breaks, and a second homology sequence B, the homology sequences A and B have at least 20 base pairs and at least 70% homology that allows for homologous recombination, together with an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence or a nucleic acid sequence encoding said enzyme. Further, all recognition sequences for site-directed induction of DNA double-strand breaks are located between homology sequences A and B. Additionally, after homologous recombination of homology sequences A and B, the resulting transgenic sequence derived from said transgenic recombination construct does not comprise any recognition site for said enzyme suitable for inducing DNA double-strand breaks (see claim 1 above).

Figure 25B of Dujon teaches that the resulting transgenic sequence from any of the transgenic events ***still contains an I-SceI site*** (see resulting sequence to the right of Figure 25B).

All claims on appeal require that the resulting transgenic sequence derived from the recombination construct does not comprise any recognition site for the enzyme suitable for inducing DNA double-strand breaks. Although this limitation is recited as a "wherein" clause, it should be properly construed as a limitation. The claims relate to a recombination system where the recognition sites are located between the homologous sequences. The recognition sites are all removed with the recombination of the homologous sequences otherwise the recombinant system would not be suitable for the repeated, successive application within the same organism. As in *Hoffer v. Microsoft Corp.*, the limitation cannot be ignored otherwise the substance of the invention would be changed. *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005) (holding that "when the 'whereby' clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."). The Examiner even acknowledges that "Dujon et al. do not teach that after recombination the resulting transgenic sequence does not contain any I-SceI site." (See Office Action mailed December 26, 2007, p. 4, first sentence). Thus, there is a fundamental difference between Dujon's teaching and the claimed subject matter.

The claims require that all recognition sequences for site-directed induction of DNA double-strand breaks are located between homology sequences A and B. First, as explained above in item 1, the description of Figure 25 discloses that the recognition sequence is located within the LTR region, rather than between homology sequences as required by the present claims. (see Dujon, col. 7, ll. 1-23). Thus the endonuclease of Dujon cuts within the homology sequence, not in between the homology sequences as required by the present claims. Further, in Dujon, given that the left I-SceI is described as being within the LTR, then the right I-SceI would be outside the LTR region. Even assuming *arguendo* that the left I-SceI was located in between two LTR sequences as alleged by the Examiner, the right I-SceI would still not be in between the LTR regions considered by the Examiner as being homologous sequences A and B. Alternatively, the Examiner contends that the right I-SceI is between two PhleoLacZ markers which allegedly correspond to homologous sequences A and B. If the PhleoLacZ markers are considered as homologous sequences A and B, then the left I-SceI is not located between these markers. If the LTR sequences are considered as homologous sequences A and B, then the right I-SceI is not located in between these LTR regions. The Examiner thus argues two alternative

sets of homologous sequences A and B, where each I-SceI is considered by the Examiner to be between different sets of allegedly homologous sequences. Given either interpretation, however, all of the recognition sites taught by Dujon are not located between homology sequences A and B as required by the claims. Thus, the Examiner has failed to provide evidence of a construct where all the recognition sites are located between the homology sequences. Analogous to the holding in *Ex parte Casey*, the Board should reverse the present obviousness rejection because of the Examiner's failure to provide this evidence. *Ex parte Casey*, Appeal 2007-2702, 2008 WL 2615596 (BPAI 2008) (where the Board reversed the obviousness rejection because the Examiner failed to provide evidence of two pooled zinc finger-encoding nucleic acids or of the structure of the nucleic acids claimed).

Furthermore, assuming *arguendo* that the structure taught by Dujon was as characterized by the Examiner, such a structure would not be suitable for the "repeated, successive application within the same organism" as required by the claims because, as depicted in Figure 25B, the resulting construct would still ***contain one I-SceI*** recognition site.[1] A recognition sequence which remains in the genome after recombination, as in Dujon, allows for further chromosomal rearrangements or deletions, which prevents the repeated, successive application of the same recombination system in the same organism that is made possible only by flanking the recognition site or sites by homologous regions. Moreover, it is further noted that Figure 25B of Dujon provides only the possible modes of recombination that may occur intra-chromosomally. Accordingly, the construct shown in Figure 25B, part 1, illustrates only an intermediate that occurs during carrying out the method, but not a recombination system for repeated and

[1] As explained in the Amendment and Reply Under 37 CFR § 1.116 dated December 30, 2008, Applicants submit that the term "for repeated, successive application within the same organism" in the preamble of claim 1 should be given patentable weight since the term gives "life, meaning, and vitality" to the claim and the term has been used to further define the claimed invention. See *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). Additionally, the term provides a fundamental characteristic of the claimed invention that is properly construed as a limitation of the claim analogous to the Federal Circuit's holding in *Poly-America LP v. GSE Lining Tech. Inc.*, 383 F.3d 1303, 1310 (Fed. Cir. 2004) ("a '[r]eview of the entirety of the '047 patent reveals that the preamble language relating to 'blown-film' does not state a purpose or an intended use of the invention, but rather discloses a fundamental characteristic of the claimed invention that is properly construed as a limitation of the claim . . . ."). Moreover, clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention. MPEP § 2111.02. See also *In re Stencel*, 828 F.2d 751 (Fed. Cir. 1987) (holding that the "purpose, set forth in the claims themselves, 'is more than a mere statement of purpose; and that language is essential to particularly point out the invention defined by the claims.'").

successive application within the same organism as claimed. Thus, the preamble is a limitation and a point of further distinction over Dujon.

From the above, the Board should find that Dujon does not teach or suggest (1) that the resulting transgenic sequence does not contain any I-SceI site(s) as required by the claims, (2) that all recognition sequences are located in between homology sequences A and B as in the present claimed system, and (3) a recombination system for the repeated, successive application within the same organism. Accordingly, for at least these three reasons, Dujon does not teach or suggest all the limitations of the claimed invention. Thus, because Dujon does not teach or suggest all limitations of the claims, the Examiner has not met his burden of establishing a *prima facie* case of obviousness.

3. Dujon does not provide any suggestion or motivation for one skilled in the art to modify the structure of Dujon.

The Examiner alleges that it would have been obvious to one skilled in the art to modify the vector of Dujon by deleting one of the I-SceI sites contained in the disclosed constructs. The Examiner contends that one of ordinary skill in the art would have been motivated to do so given the alleged teaching of Dujon that either one of the I-SceI sites alone is sufficient to produce the same recombinant transgenic sequence referring to Figure 25B part (1) and (2) of Dujon (See Final Office Action dated September 30, 2008, p. 3, and Office Action mailed December 26, 2007, p. 4). Additionally, the Examiner asserts that, because it would have been obvious to one skilled artisan to delete the right I-SceI site, the only remaining I-SceI site is located between two homologous sequences (See Final Office Action dated September 30, 2008, p. 3). Applicants respectfully disagree on the basis that the reference cited by the Examiner does not suggest or motivate the proposed modification and no basis that would lead one skill in the art to make the modification suggested is provided.

It is well established that under 35 U.S.C. § 103 the Examiner must consider the reference as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). In addition, an Examiner cannot selectively pick and choose from the disclosed parameters without proper motivation as to a particular selection. The mere fact that a

reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the prior art suggested the desirability of such modification. *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements ***in the way the claimed new invention does***." See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007) (emphasis added). Thus, it is impermissible to simply engage in a hindsight reconstruction of the claimed invention where the reference itself provides no teaching as to why the applicant's combination would have been obvious. *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

When considering Dujon as a whole, Dujon teaches that the resulting transgenic sequence from any of the transgenic events ***still contains an I-SceI site*** as seen in Figure 25B. Furthermore, Dujon at column 7, lines 1-23, explains and confirms that the resulting recombination product is found to the right in Figure 25B, which ***contains an I-SceI site***. Dujon has not provided any teaching or suggestion for modifying the resulting transgenic sequence which ***contains an I-SceI site*** to result in a transgenic sequence that ***does not comprise any recognition site*** for the enzyme suitable for inducing DNA double-strand breaks as required by the claims. Dujon provides no motivation for modifying the resulting recombination product which ***contains an I-SceI site*** to one that ***does not contain any recognition site***. One skilled in the art reading Dujon would not look to Dujon for teaching a recombinant system that results in a transgenic sequence that ***does not comprise any recognition site***, since the resulting products of Dujon all contain an I-SceI site.

The Examiner contends that because either one of the I-SceI sites alone is sufficient to produce the same recombinant transgenic sequence, it would have been obvious to delete the right I-SceI. First, Dujon contains no suggestion to do this. Moreover, even if it was done, the recombinant transgenic sequence produced would still ***contain an I-SceI site.*** See *Ex parte Whalen*, 89 U.S.P.Q.2d 1078 (BPAI 2008) (finding that "[i]n the same way, when the prior art teaches away from the claimed solution as presented here . . ., obviousness cannot be proven

merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition."). No reason has been provided why one of skill in the art would delete the right I-SceI. Further, the Examiner has failed to provide evidence of a recombinant sequence without a recognition site. See *Ex parte Casey*, Appeal 2007-2702, 2008 WL 2615596 (BPAI 2008) (where the Board reversed the obviousness rejection because the Examiner failed to provide evidence of two pooled zinc finger-encoding nucleic acids or of the structure of the nucleic acids as claimed). There is also nothing in Dujon to lead one skilled in the art to select or modify the vector to obtain a recombinant sequence without a recognition site. Dujon does not teach or suggest a vector comprising, in the 5' to 3' direction, a copy of the LTR-I-SceI-selection marker unit and an additional copy of a similar unit having the I-SceI site deleted. Thus, because Dujon has not taught such a modification or suggested the desirability of such modification, Dujon does not render the claims obvious without impermissible hindsight.

4. Even if the structure were modified as suggested by the Examiner, one skilled in the art would not arrive at the claimed invention.

The Examiner suggested modifying the vector of Dujon by deleting the right I-SceI site that was alleged as not being needed to practice the invention shown in part 1) of Figure 25B. However, even with the modification suggested by the Examiner, one skilled in the art would not arrive at the claimed invention.

The Examiner characterizes the right I-SceI as being between two PhleoLacZ markers which allegedly correspond to homologous sequences A and B. Following the teaching of Dujon, to delete the right I SceI site, the right I SceI site would be cut and the PhleoLacZ markers would recombine as in part 2) of Figure 25B. In the construct as characterized by the Examiner, an LTR sequence is also located between the two PhleoLacZ markers. Thus with the recombination of the markers to delete the right I-SceI, the LTR sequence between the markers would also be deleted. Therefore, if the right I-SceI site were to be deleted following the teaching of Dujon, there would only be one LTR region remaining and the left I-SceI would not be in between two homologous sequences and the vector would not be capable of homologous

recombination as required by the claimed system. One skilled in the art making the modification suggested by the Examiner would not arrive at the claimed invention.

Moreover, even if the right I-SceI site was to be deleted as suggested by the Examiner, based on the teachings of Dujon, the recombinant transgenic sequence produced would still ***contain an I-SceI site*** as explained above.

5. The modification suggested by the Examiner renders the structure inoperable for its intended purpose.

If the right I-SceI site of Dujon's construct were to be deleted as suggested by the Examiner, then the modes of recombination as proposed in Figure 25B would be inoperative.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (The court reversed an obviousness rejection stating that the "suggested combination of references [or modification] would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813). MPEP § 2143.02 VI.

Assuming *arguendo* that the structure taught by Dujon was as characterized by the Examiner, if the right I-SceI site were to be deleted as suggested by the Examiner, the PhleoLacZ markers would recombine as in part 2) of Figure 25B, and the LTR sequence between the markers would also be deleted resulting in only one LTR region remaining as explained above. Similarly, as explained above, if the left I-SceI were to be deleted, then the marker between the LTR regions would also be deleted resulting in only one PhleoLacZ marker remaining. Under either alternative, with only one of the alleged homologous sequences remaining with either of the I-SceI sites deleted, the resulting vector would not be capable of homologous recombination and the further modes of recombination as proposed in Figure 25B would be inoperative. Contrary to the Examiner's assertion, one skilled in the art could not practice the invention of part 1) given that only one LTR region would be remaining if the right I-SceI were deleted, thus

preventing any homologous recombination. Contrary to the Examiner's assertion, Dujon would not have led the skilled artisan, upon recognizing such inoperability, to modify the vector by deleting the right I-SceI site, since the construct would no longer function in the disclosed scheme.

Dujon does not teach or suggest deleting the right I-SceI as suggested by the Examiner or a recombinant transgenic sequence without a I-SceI. Dujon does not teach or suggest a vector comprising, in the 5' to 3' direction, a copy of the LTR-I-SceI-selection marker unit and an additional copy of a similar unit having the I-SceI site deleted. Thus, there are structural as well as use differences between the present claims and the reference. To arrive at such a vector, one skilled in the art would have to rearrange the elements taught in Dujon to operate for a different purpose than that which is disclosed and which the reference does not suggest. Therefore, Dujon does not render the claims obvious within the meaning of 35 U.S.C. § 103 for this additional reason.

In sum, because the Examiner's characterization of the structure allegedly taught in Dujon is inaccurate, because all the limitations of the claims are not taught, because the proposed modification would still not lead one skilled in the art to arrive at the claimed invention and would render the system inoperable, and because the proposed modification would change the principle of operation of the Dujon invention being modified, reversal of the obviousness rejections is respectfully requested for claim 1 and the claims dependent therefrom. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious).

Claim 3

Claim 3 depends indirectly from claim 1 adding the limitation that the construct, after the first homology sequence, contains a further nucleic acid sequence (as in claim 2) and further contains a second recognition sequence for the site-directed induction of DNA double-strand breaks. Because claim 3 depends from claim 1, all the features of claim 1 are incorporated into claim 3. Therefore, the limitation that all recognition sequences for site-directed induction of DNA double-strand breaks are located between homology sequences A and B of claim 1 would also apply to the second recognition sequence recited in claim 3.

In addition to the arguments with respect to claims 1, 2, 4, and 27-28 above, Dujon does not teach or suggest two recognition sequences located between homology sequences A and B as required by claim 3. Furthermore, even if one skilled in the art would have been motivated to delete the right I-SceI site as suggested by the Examiner, such a modification would not result in the system as claimed in claim 3 comprising two recognition sequences between homology sequences A and B. The Examiner asserts that if the right I-SceI site was deleted as he suggests, the only I-SceI site left would be located between two homologous sequences (See Final Office Action dated September 30, 2008, p. 3). Therefore, the Examiner acknowledges that only one recognition sequence would be located between two homology sequences with the Examiner's suggested deletion of the right I-SceI.

Moreover, assuming *arguendo* that two recognition sites were suggested, if more than one I-Sce I site is cut in the construct of Dujon, no homology region is even available. The end joining described in Figure 25 B3 of Dujon only repairs the ends and the resulting recombination product results in a solitary LTR, not homologous recombination of the homology sequences as claimed.

Thus, because Dujon does not teach or suggest all limitations of claim 3, the Examiner has not met his burden of establishing a *prima facie* case of obviousness. Reversal of the obviousness rejection is respectfully requested.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A. As indicated above, the claims in Appendix A include the amendments filed by Applicants on May 27, 2008, and do not include the amendments filed on December 30, 2008.

IX. EVIDENCE

No evidence submitted pursuant to 37 C.F.R. §§ 1.130, 1.131, or 1.132 is being relied upon for this appeal. Accordingly, no such evidence is provided in APPENDIX B.

X. RELATED PROCEEDINGS

As stated in section II, *supra*, no related proceedings have been or are now pending. Accordingly, no related decisions are provided in APPENDIX C.

XI. CONCLUSION

In sum, for the reasons discussed above, reversal of the obviousness rejections under 35 U.S.C. § 103(a) of claims 1-4 and 27-28 is strongly urged.

This Appeal Brief is filed within the two month period from the date of filing the Notice of Appeal to and including April 27, 2009 pursuant to 37 CFR § 41.37(a), with the required fee authorization pursuant to 37 CFR § 41.20(b)(2). No further fee is believed due. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 13173-00010-US from which the undersigned is authorized to draw.

Dated: April 27, 2009

Respectfully submitted,

By

Roberte M. D. Makowski, Ph.D.
Registration No.: 55,421
CONNOLLY BOVE LODGE & HUTZ LLP
1007 North Orange Street
P.O. Box 2207
Wilmington, Delaware 19899
(302) 658-9141
(302) 658-5614 (Fax)
Attorneys for Appellants

680266

APPENDIX A

Claims Involved in the Appeal of Application Serial No. 10/750,891

1. (Previously presented) A recombination system for repeated, successive application within the same organism comprising:

a transgenic recombination construct capable of being inserted into the chromosomal DNA of a cukaryotic organism said construct comprising in a 5'- to 3'-orientation;

a first homology sequence A;

at least one recognition sequence for site-directed induction of DNA double-strand breaks where all recognition sequences for site-directed induction of DNA double-strand breaks are located between homology sequences A and B; and

a second homology sequence B,

wherein the homology sequences A and B have at least 20 base pairs and at least 70% homology that allows for homologous recombination; and

an enzyme suitable for inducing DNA double-strand breaks at a recognition sequence for the site-directed induction of DNA double-strand breaks or a nucleic acid sequence encoding said enzyme;

wherein after homologous recombination of homology sequences A and B the resulting transgenic sequence derived from said transgenic recombination construct does not comprise any recognition site for said enzyme suitable for inducing DNA double-strand breaks.

2. (Previously presented) The system of claim 1, wherein the construct, after said first homology sequence, contains a further nucleic acid sequence.

3. (Previously presented) The system of claim 2, wherein the construct further contains a second recognition sequence for the site-directed induction of DNA double-strand breaks.

4. (Previously presented) The system of claim 2, wherein the further nucleic acid sequence contains at least one selection marker.

5. (Withdrawn) The system of claim 1, wherein the construct further contains at least one of the elements selected from the group consisting of selection markers, reporter genes, replication origins, multiple cloning regions, border sequences for Agrobacterium transfection, sequences which enable homologous recombination or insertion into a genome of a host organism, expression cassette for an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence for the site-directed induction of DNA double-strand breaks and combinations thereof.

6. (Withdrawn) The system of claim 1, wherein the enzyme is selected from the group consisting of restriction endonucleases, homing endonucleases, group II intron endonucleases, recombinases, transposases, chimeric nucleases and combinations thereof.

7. (Withdrawn) The system of claim 1, wherein the enzyme is selected from the group consisting of F-SceI, F-SceII, F-SuvI, F-TevI, F-TevII, I-AmaI, I-AniI, I-CeuI, I-CeuAIIP, I-ChuI, I-CmoeI, I-CpaI, I-CpaII, I-CreI, I-CrepsbIP, I-CrepsbIIP, I-CrepsbIIIP, I-CrepsbIVP, I-CsmI, I-CvuI, I-CvuAIP, I-DdiI, I-DdiII, I-DirI, I-DmoI, I-HmuI, I-HmuII, I-HspNIP, I-LlaI, I-MsoI, I-NaaI, I-NanI, I-Nc1IP, I-NgrIP, I-NitI, I-NjaI, I-Nsp236IP, I-PakI, I-PboIP, I-PcuIP, I-PcuAI, I-PcuVI, I-PgrIP, I-PobIP, I-PorI, I-PorIIP, I-PpbIP, I-PpoI, I-SPBetaIP, I-ScaI, I-SceI, I-SceII, I-SceIII, I-SceIV, I-SceV, I-SceVI, I-SceVII, I-SexIP, I-SneIP, I-SpomCP, I-SpomIP, I-SpomIIP, I-SquIP, I-Ssp6803I, I-SthPhiJP, I-SthPhiST3P, I-SthPhiS3bP, I-TdeIP, I-TevI, I-TevII, I-TevIII, I-UarAP, I-UarHGPA1P, I-UarHGPA13P, I-VinIP, I-ZbiIP, PI-MtuI, PI-MtuHIP, PI-MtuHIIP, PI-PfuI, PI-PfuII, PI-PkoI, PI-PkoII, PI-PspI, PI-Rma43812IP, PI-SPBetaIP, PI-SceI, PI-TfuI, PI-TfuII, PI-ThyI, PI-TliI, PI-TliII and combinations thereof.

8. (Withdrawn) The system of claim 1, wherein the enzyme is selected from the group consisting of enzymes encoded by the sequence as shown in SEQ ID NO: 2, 4, 6, 8 or 10, and combinations thereof.

9. (Withdrawn) The system of claim 1, wherein the enzyme is expressed from an expression cassette that contains a nucleic acid sequence encoding said enzyme.

10. (Withdrawn) The system of claim 9, wherein the nucleic acid sequence encoding said enzyme comprises the sequence as shown in SEQ ID NO: 1, 3, 5, 7 or 9.

11. (Withdrawn) A method for removing a DNA sequence from chromosomal DNA of a eukaryotic cell or organism comprising:

introducing the recombination system of claim 1 into the chromosomal DNA of a eukaryotic cell or organism;

inducing DNA double-strand breaks at the recognition sequence; and

conducting homologous recombination between the homology sequences A and B.

12. (Withdrawn) The method of claim 11, wherein the construct contains a further nucleic acid sequence.

13. (Withdrawn) The method of claim 12, wherein the further nucleic acid sequence contains at least one of the elements selected from the group consisting of selection markers, reporter genes, replication origins, multiple cloning regions, border sequences for Agrobacterium transfection, sequences which enable homologous recombination or insertion into a genome of a host organism, expression cassette for an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence for the site-directed induction of DNA double-strand breaks and combinations thereof.

14. (Withdrawn) The method of claim 11, wherein the construct, after said first homology sequence A contains a second recognition sequence for the site-directed induction of DNA double-strand breaks.

15. (Withdrawn) The method of claim 11, wherein the construct contains at least one of the elements selected from the group consisting of selection markers, reporter genes, replication origins, multiple cloning regions, border sequences for Agrobacterium transfection, sequences which enable homologous recombination or insertion into a genome of a host organism, expression cassette for an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence for the site-directed induction of DNA double-strand breaks and combinations thereof.

16. (Withdrawn) The method of claim 11, wherein the enzyme is selected from the group consisting of restriction endonucleases, homing endonucleases, recombinases, transposases, chimeric nucleases and combinations thereof.

17. (Withdrawn) The method of claim 11, wherein the enzyme is selected from the group consisting of F-SceI, F-SCeII, F-SuvI, F-TevI, F-TevII, I-AmaI, I-AniI, I-CeuI, I-CeuAIIP, I-ChuI, I-CmoeI, I-CpaI, I-CpaII, I-CreI, I-CrepsbIP, I-CrepsbIIP, I-CrepsbIIIP, I-CrepsbIVP, I-CsmI, I-CvuI, I-CvuAIP, I-DdiI, I-DdiII, I-DirI, I-DmoI, I-HmuI, I-HmuII, I-HspNIP, I-LlaI, I-MsoI, I-NaaI, I-NanI, I-Nc1IP, I-NgrIP, I-NitI, I-NjaI, I-Nsp236IP, I-PakI, I-PboIP, I-PcuIP, I-PcuAI, I-PcuVI, I-PgrIP, I-PobIP, I-PorI, I-PorIIP, I-PpbIP, I-PpoI, I-SPBetaIP, I-ScaI, I-SceI, I-SceII, I-SceIII, I-SceIV, I-SceV, I-SceVI, I-SceVII, I-SexIP, I-SneIP, I-SpomCP, I-SpomIP, I-SpomIIP, I-SquIP, I-Ssp6803I, I-SthPhiJP, I-SthPhiST3P, I-SthPhiS3bP, I-TdeIP, I-TevI, I-TevII, I-TevIII, I-UarAP, I-UarHGPA1P, I-UarHGPA13P, I-VinIP, I-ZbiIP, PI-MtuI, PI-MtuHIP, PI-MtuHIIP, PI-PfuI, PI-PfuII, PI-PkoI, PI-PkoII, PI-PspI, PI-Rma43812IP, PI-SPBetaIP, PI-SceI, PI-TfuI, PI-TfuII, PI-ThyI, PI-ThiI, PI-TliII and combinations thereof.

18. (Withdrawn) The method of claim 11, wherein the enzyme is selected from the group consisting of enzymes that contain the sequence as shown in SEQ ID NO: 2, 4, 6, 8 or 10, and combinations thereof.

19. (Withdrawn) The method of claim 11, wherein the enzyme is encoded in an expression cassette.

20. (Withdrawn) The method of claim 11, wherein the nucleic acid sequence comprises the sequence as shown in SEQ ID NO: 1, 3, 5, 7 or 9, or a combination thereof.

21. (Withdrawn) An organism comprising the recombination system of claim 1.

22. (Withdrawn) The organism of claim 21 selected from the group consisting of yeasts, algae, fungi and animal and plant organisms.

23. (Cancelled)

24. (Withdrawn, currently amended) The organism of claim ~~22~~ 21, wherein the plant organism is selected from the group consisting of Arabidopsis thaliana, tobacco, wheat, rye, barley, oats, oilseed rape, maize, potato, sugar beet, soybean, sunflower, pumpkin/squash and peanut.

25. (Withdrawn) A cell culture, organ, tissue, part or transgenic propagation material derived from the organism of claim 21.

26. (Withdrawn) A method for the production of foodstuff, feedstuff, seeds, pharmaceuticals or fine chemicals comprising expressing said foodstuff, feedstuff, seeds, pharmaceuticals or fine chemicals from the recombinant system of the organism of claim 20.

27. (Previously presented) The system of claim 2, wherein the further nucleic acid sequence comprises an expression cassette for an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence for the site-directed induction of DNA double-strand breaks.

28. (Previously presented) The system of claim 1, wherein the construct further comprises an expression cassette for an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence for the site-directed induction of DNA double-strand breaks.

29. (Withdrawn) The method of claim 12, wherein the further nucleic acid sequence comprises an expression cassette for an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence for the site-directed induction of DNA double-strand breaks.

30. (Withdrawn) The method of claim 11, wherein the construct comprises an expression cassette for an enzyme suitable for inducing DNA double-strand breaks at the recognition sequence for the site-directed induction of DNA double-strand breaks.

APPENDIX B

None.

APPENDIX C

None.